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canceled claims, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**


REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-12, 16, 18-26, 37, and 38 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter not described in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner alleges that the specification fails "to enable one to determine which compounds other than those of claims 13 and 14 are intended to be able to inhibit enzyme mediated-cleavage of the polynucleotide substrate."

Solely to facilitate prosecution and not acquiescing to the Examiner's enablement rejection, the Applicants have canceled claims 1-12, 16, 18-26, 37, and 38 without prejudice thus rendering this rejection moot.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-12, 16, 18-26, 37, and 38, have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that "the scope of the compounds intended to be used to inhibit enzyme-mediated cleavage of a polynucleotide substrate is unclear since the specification fails to teach one skilled in the art,



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which compounds other than those in claims 13 and 14, would satisfy the requirements for the method."

Solely to facilitate prosecution and not acquiescing to the Examiner's indefiniteness rejection, the Applicants have canceled claims 1-12, 16, 18-26, 37, and 38 without prejudice thus rendering this rejection moot.

REJECTIONS UNDER 35 U.S.C. §103(a)


Claims 16-18 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Coates, *et al.* Solely to facilitate prosecution and not acquiescing to the Examiner's indefiniteness rejection, the Applicants have canceled claims 16-18 without prejudice thus rendering this rejection moot.

OBJECTION TO CLAIMS

Claims 13-15 are objected to for depending from rejected claims. Applicants have amended these claims to be in independent form therefore rendering the objection moot.

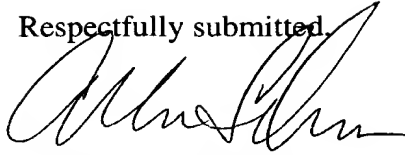
The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned agent.



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Respectfully submitted,



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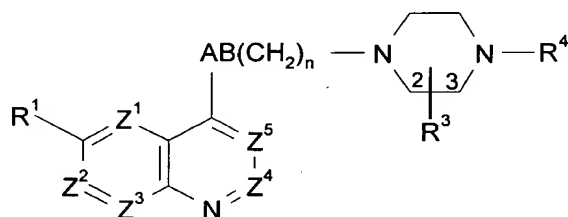


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In the Claims:

13. (Amended) A method of modulating the activity of a mammalian type II topoisomerase enzyme comprising contacting said enzyme with[The method according to claim 1, wherein said compound is] a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof:



(Ia)

wherein:

one of Z¹, Z², Z³, Z⁴ and Z⁵ is N, one is CR^{1a} and the remainder are CH, or one of Z¹, Z², Z³, Z⁴ and Z⁵ is CR^{1a} and the remainder are CH;

R¹ is selected from hydroxy; (C₁₋₆) alkoxy optionally substituted by (C₁₋₆)alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, NH₂CO, hydroxy, thiol, (C₁₋₆)alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C₁₋₆)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted (C₁₋₆)alkyl; halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; nitro; azido; acyl; acyloxy; acylthio; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, or when one of Z¹, Z², Z³, Z⁴ and Z⁵ is N, R¹ may instead be hydrogen;

R^{1a} is selected from H and the groups listed above for R¹;

R³ is hydrogen; or

R³ is in the 2- or 3-position and is:

carboxy; (C₁₋₆)alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenylloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R¹⁰; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-

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thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R¹⁰; or 5-oxo-1,2,4-oxadiazol-3-yl; or

R³ is in the 2- or 3-position and is (C₁₋₄)alkyl or ethenyl substituted with any of the groups listed above for R³ and/or 0 to 3 groups R¹² independently selected from:

thiol; halogen; (C₁₋₆)alkylthio; trifluoromethyl; azido; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; provided that when R³ is disubstituted with hydroxy or amino and carboxy containing substituents these may optionally together form a cyclic ester or amide linkage, respectively;

wherein R¹⁰ is selected from (C₁₋₄)alkyl; (C₂₋₄)alkenyl; aryl; a group R¹² as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₁₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; cyano; or tetrazolyl;

R⁴ is a group -CH₂-R⁵ in which R⁵ is selected from:

(C₃₋₁₂)alkyl; hydroxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkoxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkanoyloxy(C₃₋₁₂)alkyl; (C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; hydroxy-, (C₁₋₁₂)alkoxy- or (C₁₋₁₂)alkanoyloxy-(C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; cyano(C₃₋₁₂)alkyl; (C₂₋₁₂)alkenyl; (C₂₋₁₂)alkynyl; tetrahydrofuryl; mono- or di-(C₁₋₁₂)alkylamino(C₃₋₁₂)alkyl; acylamino(C₃₋₁₂)alkyl; (C₁₋₁₂)alkyl- or acyl-aminocarbonyl(C₃₋₁₂)alkyl; mono- or di-(C₁₋₁₂)alkylamino(hydroxy)(C₃₋₁₂)alkyl; optionally substituted phenyl(C₁₋₂)alkyl, phenoxy(C₁₋₂)alkyl or phenyl(hydroxy)(C₁₋₂)alkyl; optionally substituted diphenyl(C₁₋₂)alkyl; optionally substituted phenyl(C₂₋₃)alkenyl; optionally substituted benzoyl or benzoyl(C₁₋₃)alkyl; optionally substituted heteroaryl or heteroaryl(C₁₋₂)alkyl; and optionally substituted heteroaryl or heteroarylmethyl;

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n is 0, 1 or 2;

AB is NR^{11}CO , $\text{CO-CR}^8\text{R}^9$ or $\text{CR}^6\text{R}^7\text{-CR}^8\text{R}^9$ or when n is 1 or 2, AB may instead be $\text{O-CR}^8\text{R}^9$ or $\text{NR}^{11}\text{-CR}^8\text{R}^9$, or when n is 2 AB may instead be $\text{CR}^6\text{R}^7\text{-NR}^{11}$ or $\text{CR}^6\text{R}^7\text{-O}$, provided that when n is 0, B is not CH(OH) ,

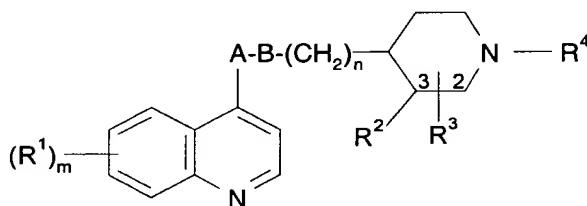
and wherein:

each of R^6 and R^7 , R^8 and R^9 is independently selected from: H; thiol; (C_{1-6}) alkylthio; halo; trifluoromethyl; azido; (C_{1-6}) alkyl; (C_{2-6}) alkenyl; (C_{1-6}) alkoxycarbonyl; (C_{1-6}) alkylcarbonyl; (C_{2-6}) alkenyloxycarbonyl; (C_{2-6}) alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3 ; (C_{1-6}) alkylsulphonyl; (C_{2-6}) alkenylsulphonyl; or (C_{1-6}) aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6}) alkyl or (C_{1-6}) alkenyl; or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined; and each R^{11} is independently H, trifluoromethyl, (C_{1-6}) alkyl, (C_{1-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, (C_{1-6}) alkylcarbonyl, aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6}) alkoxycarbonyl, (C_{1-6}) alkylcarbonyl, (C_{1-6}) alkenyloxycarbonyl, (C_{2-6}) alkenylcarbonyl, (C_{1-6}) alkyl or (C_{1-6}) alkenyl and optionally further substituted by (C_{1-6}) alkyl or (C_{1-6}) alkenyl;

or where one of R^3 and R^6 , R^7 , R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.[.]

wherein the said compound inhibits enzyme-mediated cleavage of a polynucleotide substrate.

14. (Amended) A method of modulating the activity of a mammalian type II topoisomerase enzyme comprising contacting said enzyme with a compound of formula (Ib)[The method according to claim 1], wherein said compound is:



(Ib)

wherein:

m is 1 or 2

each R^1 is independently hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6}) alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6}) alkyl, acyl or (C_{1-6}) alkylsulphonyl groups, NH_2CO , hydroxy, thiol, (C_{1-6}) alkylthio, heterocyclythio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6}) alkyl;

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6)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted (C₁₋₆)alkyl; halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; nitro; azido; acyl; acyloxy; acylthio; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups; either R² is hydrogen; and

R³ is in the 2- or 3-position and is hydrogen or (C₁₋₆)alkyl or (C₂₋₆)alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C₁₋₆)alkylthio; trifluoromethyl; azido; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; or

R³ is in the 3-position and R² and R³ together are a divalent residue =CR⁵¹R⁶¹ where R⁵¹ and R⁶¹ are independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, aryl(C₁₋₆)alkyl and aryl(C₂₋₆)alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R³;

R⁴ is a group -CH₂-R⁵ in which R⁵ is selected from:

(C₃₋₁₂)alkyl; hydroxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkoxy(C₃₋₁₂)alkyl; (C₁₋₁₂)alkanoyloxy(C₃₋₁₂)alkyl; (C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; hydroxy-, (C₁₋₁₂)alkoxy- or (C₁₋₁₂)alkanoyloxy-(C₃₋₆)cycloalkyl(C₃₋₁₂)alkyl; cyano(C₃₋₁₂)alkyl; (C₂₋₁₂)alkenyl; (C₂₋₁₂)alkynyl; tetrahydrofuryl; mono- or di-(C₁₋₁₂)alkylamino(C₃₋₁₂)alkyl; acylamino(C₃₋₁₂)alkyl; (C₁₋₁₂)alkyl- or acyl-aminocarbonyl(C₃₋₁₂)alkyl; mono- or di-(C₁₋₁₂)alkylamino(hydroxy) (C₃₋₁₂)alkyl; optionally substituted phenyl(C₁₋₂)alkyl, phenoxy(C₁₋₂)alkyl or phenyl(hydroxy)(C₁₋₂)alkyl; optionally substituted diphenyl(C₁₋₂)alkyl; optionally substituted phenyl(C₂₋₃)alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C₁₋₂)alkyl; and optionally substituted heteroaroyl or heteroaroylmethyl;

n is 0, 1 or 2;

A is NR¹¹, O, S(O)_x or CR⁶R⁷ and B is NR¹¹, O, S(O)_x or CR⁸R⁹ where x is 0, 1 or 2 and wherein:

each of R⁶ and R⁷ R⁸ and R⁹ is independently selected from: H; thiol; (C₁₋₆)alkylthio; halo; trifluoromethyl; azido; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋

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6)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₁₋₆)alkenyl;
or R⁶ and R⁸ together represent a bond and R⁷ and R⁹ are as above defined;
or R⁶ and R⁸ together represent -O- and R⁷ and R⁹ are both hydrogen;
or R⁶ and R⁷ or R⁸ and R⁹ together represent oxo;
and each R¹¹ is independently H, trifluoromethyl, (C₁₋₆)alkyl, (C₁₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₁₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl or (C₁₋₆)alkenyl and optionally further substituted by (C₁₋₆)alkyl or (C₁₋₆)alkenyl;
provided that A and B cannot both be selected from NR¹¹, O and S(O)_x and when one of A and B is CO the other is not CO, O or S(O)_x[.]

wherein the said compound inhibits enzyme-mediated cleavage of a polynucleotide substrate.

15. (Amended) A method of modulating the activity of a mammalian type II topoisomerase enzyme comprising contacting said enzyme with a compound[The method according to claim 1], wherein said compound is selected from the group consisting of:

[3R,4R]-3-Ethyl-1-heptyl-4-[3-(R,S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine;

[3R,4R]-1-Heptyl-3-(1-(R)-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine;

[3R,4R]-1-Heptyl-3-hydroxymethyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine;

[2S]-1-Heptyl-4-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)ethyl]-2-hydroxymethylpiperazine;

[2S]-2-Carboxymethyl-1-heptyl-4-[2-(R,S)-hydroxy-2-(6-methoxyquinolin-4-yl)ethyl]piperazine trihydrochloride; and

1-Hydroxyheptyl-4-[2-(R)-hydroxy-2-(6-methoxyquinolin-4-yl)ethyl]piperazine, [.]

wherein the said compound inhibits enzyme-mediated cleavage of a polynucleotide substrate.